Alerts, Notices, and Case Reports

'Crystal' and Pregnancy Methamphetamine-Associated Maternal Deaths

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ALTHOUGH COCAINE AND OPIATES have attracted greater interest in the literature and in the popular press, amphetamines are abused by pregnant women in California with nearly the same frequency as cocaine; among white women, abuse of amphetamine is more common than that of cocaine.[1]

In a recently published statewide study of the prevalence of drug abuse,[1] 29,494 women had toxicologic screens done during labor. The most commonly detected illicit drugs were cannabinoids (1.88% of patients), cocaine (1.11%), and amphetamines (0.66%). Among the 10,615 white, non-Hispanic patients tested, 1.32% had a positive screen for amphetamines, with 0.60% testing positive for cocaine. In this study, the rates were 20-fold higher for both amphetamine and cocaine abuse among smokers than among nonsmokers and more than 10-fold higher among patients not receiving prenatal care than among those having prenatal care.

Amphetamines have been reported to be the most common drugs of abuse in nonpregnant patients in San Diego County and among pregnant women delivering at the University of California, San Diego (UCSD).[2,3] Our experience in the private hospital setting is similar to that at UCSD and reported statewide—among white, non-Hispanic patients, amphetamines appear to be the drug of choice for abuse during pregnancy.

In our obstetric patients, virtually all toxicologic screens positive for amphetamines also show methamphetamines, and patients who admit using amphetamines say that they are using "crystal" or "ice," a highly purified crystalline form of methamphetamine. We report the details of two cases of maternal deaths associated with the abuse of methamphetamine and discuss the myriad of possible adverse effects of crystal use during pregnancy.

Report of Cases

Case 1

The patient, a 26-year-old multipara, was admitted in labor with severe abdominal pain at 37 weeks' gestation. During the pregnancy, the patient had missed numerous prenatal visits and admitted using marijuana, crystal, and occasionally alcohol. The prenatal course had been remarkable only for poor weight gain. The patient had no underlying medical problems.

At the time of admission, the patient had severe and constant contractions. The blood pressure was 120/80 mm of mercury, and the pulse rate was 110 beats per minute. The fetus could not be adequately monitored because of maternal discomfort. The cervix was dilated 4 cm and 80% effaced. Membranes ruptured shortly after admission; thick meconium was present.

Eight minutes after admission, the patient became cyanotic and unresponsive, with gasping respirations. Within two minutes, she had a cardiorespiratory arrest. Electromechanical dissociation was present. Resuscitation included intubation, ventilation, chest compressions, the administration of fluids, inotropic agents, and pressors, and transthoracic pacing. These efforts were unsuccessful. Fifteen minutes after the initiation of cardiopulmonary resuscitation, a cesarean section was done. The infant weighed 2,740 grams and had Apgar scores of 0, 0, 3, 3, and 4 at 1, 5, 10, 15, and 20 minutes, respectively.

Resuscitative efforts for the patient were discontinued after 30 minutes. An autopsy showed amniotic fluid debris in the pulmonary vasculature. The serum methamphetamine concentration measured from a postmortem specimen was 1.8 mg per ml, and the amphetamine level was 0.3 μg per ml. The medical examiner judged the cause of death to be amniotic fluid embolism due to methamphetamine abuse.

The newborn had a stormy course in the intensive care unit, with hypotonia and seizures. He was discharged home on day 31 to the patient's family.

Case 2

The patient, a 25-year-old multipara, was brought to the hospital by ambulance at 37 weeks' gestation with a history of obtundation and seizures for three hours.

The patient had had a single prenatal visit and had planned to give the baby up for adoption. She had no known medical problems. She was normotensive in the physician's office two weeks before being admitted to the hospital.

At admission, her blood pressure was 150/96 mm of mercury, and the pulse rate was 108 beats per minute. Her pupils were 3 mm and fixed, with no corneal reflexes. The patient was unresponsive to any but deep pain and showed decerebrate posturing. Within minutes of arrival, her membranes ruptured and a 2,480-gram male infant with Apgar scores of 8 and 9 was rapidly delivered. The placenta showed a large, fresh area of abruption.

After intravenous access had been established, the patient was given magnesium sulfate, an endotracheal tube was introduced, and she was ventilated. An emer-

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
HELLP [syndrome] = *h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelet count
UCSD = University of California, San Diego

gency computed tomographic (CT) scan (Figure 1) showed a large intracranial hemorrhage originating in the basal ganglia, tracking in a subependymal location, and breaking into the ventricular system. Cerebral edema was present. Laboratory studies revealed trace protein on a dipstick urinalysis, a hematocrit of 0.36 (36%), a platelet count of 26×10^9 per liter (26,000 per mm^3), and the following serum levels: aspartate aminotransferase, 2,100 units per liter; alanine aminotransferase, 750 units per liter; lactate dehydrogenase, 3,100 units per liter; creatinine, 100 μmol per liter (1.1 mg per dl); and bilirubin, 34 μmol per liter (2.0 mg per dl). The initial diagnosis was eclampsia, the HELLP syndrome [*h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelet count], and intracranial hemorrhage.

The patient was transfused with platelets and treated with phenytoin (Dilantin) as prophylaxis against further seizures. The blood pressure stabilized at 130/80 mm of mercury, and no antihypertensive treatment was required. Despite receiving mannitol, the patient was unresponsive. An intracranial pressure monitor was placed. Treatment included therapeutic hyperventilation and the administration of dexamethasone sodium phosphate (Decadron) and more mannitol, but the intracranial pressure could not be controlled and rose above the mean arterial pressure. A follow-up CT scan showed virtual obliteration of the ventricles. An electroencephalogram showed bilateral epileptiform activity and severe diffuse nonspecific abnormalities. After extensive discussion with the family, support was discontinued on day 8.

A urine specimen obtained at the time of admission showed amphetamines and methamphetamines. The father of the baby, who had initially denied any drug use, admitted that he, the patient, and several friends had smoked crystal and marijuana on the night and early morning before the woman's admission to the hospital.

Autopsy examination established the immediate cause of death as intracerebral hemorrhage originating in the left basal ganglia with extension into both lateral ventricles, cerebral edema, and tonsillar herniation. The underlying causes were judged by the medical examiner to be methamphetamine abuse and preeclampsia.

The infant did well. He had the mild transient hypoglycemia and tachypnea of newborns. A sonogram of his brain was normal. The adoptive parents were fully apprised of the situation, and the infant was discharged home to them on day 6.

Discussion

Methamphetamine is a potent, inexpensive, long-acting psychoactive drug. A highly purified form, crystalline methamphetamine ("crystal," "ice," "crank") is easily synthesized. Unlike its predecessor, "speed," which could be ingested or injected, crystal can be smoked or inhaled and is said to produce an extraordinarily long-lasting euphoric state. Methamphetamine in any form has various dangerous and possibly lethal side effects.[4,5]

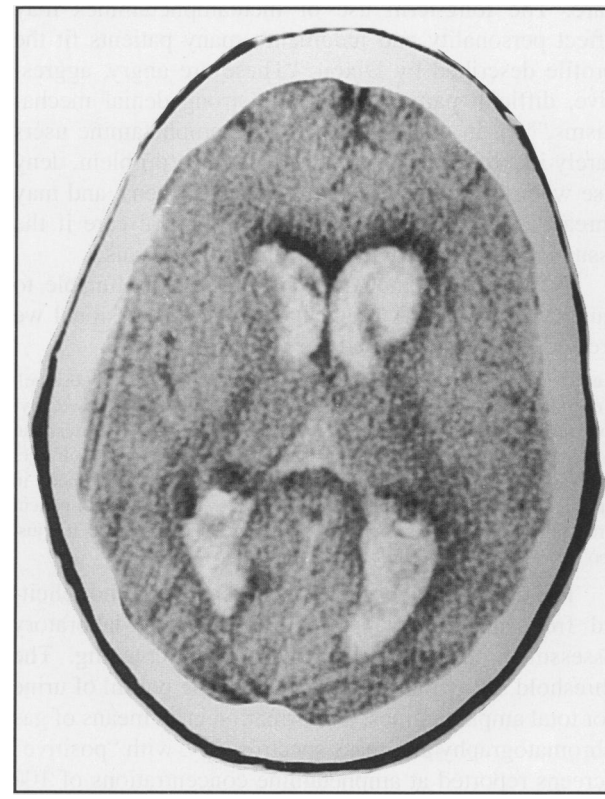

Figure 1.—A computed tomographic scan of the brain shows an acute left basal ganglia hemorrhage and a massive amount of intraventricular blood.

Methamphetamine drives the release of catecholamines and dopamine from the presynaptic nerve ending and inhibits presynaptic uptake and degradation of these substances.[5] In addition, methamphetamine depletes catecholamine reserves in the presynaptic terminal. Pharmacologic effects include both α- and β-adrenergic stimulation, including increased blood pressure, pulse rate, cardiac output, and systemic vascular resistance. The immediate toxic effects may include severe hypertension and hypertensive crisis, cerebrovascular accident due to vasospasm, intracranial hemorrhage, cardiac arrhythmias, pulmonary edema, agitation, confusion, seizures, hyperpyrexia, and cardiovascular collapse. Long-term effects may include anorexia, weight loss, aggressive behavior, amphetamine-induced psychosis, and cerebral arteritis.[5,6]

Epidemiologic studies have identified clear risk factors for methamphetamine abuse during pregnancy.[1,3] These risk factors include white, non-Hispanic ethnic background, cigarette smoking, and little or no prenatal

care. The long-term use of methamphetamines may affect personality and judgment[6]; many patients fit the profile described by Dixon: "These are angry, aggressive, difficult parents who have strong denial mechanisms."[3(p440)] In our experience, methamphetamine users rarely identify their substance abuse as a problem, deny use when it is detected by toxicology screens, and may threaten to or actually discontinue prenatal care if the issue is brought up by health care professionals.

Even a highly motivated patient may be unable to quit using crystal. A pregnant medical professional we treated recently described her addiction thus:

I used drugs in my teens—dope, acid, angel dust, and coke [cocaine]. I even used IV heroin. But I could quit, and I did. I hadn't used anything for six years. Then I tried crystal just once. It was better than heroin, better than cocaine, better than anything. . . . Now I can't get it out of my mind. I'm thinking about it all the time. I've been in drug rehab twice before, and I know as soon as I get out [of in-patient drug rehabilitation] this time, I'll be going back to crystal. It's just too strong.

The detection of methamphetamine use, if not elicited from the patient, is accomplished by laboratory assessment, usually urine toxicologic screening. The threshold set by our laboratory is 300 ng per ml of urine for total amphetamines. Confirmation is by means of gas chromatography and mass spectroscopy, with "positive" screens reported at amphetamine concentrations of 100 ng per ml and methamphetamine concentrations of 100 ng per ml. The threshold for detection by gas chromatography is substantially lower, and a patient who used amphetamines, even in large amounts, a day or two before may have a negative urine screen. Blood levels are seldom used, except by forensic pathologists. Deaths have been reported after intravenous or oral administration of methamphetamine, with levels ranging as high as 1.3 μg per ml.[7]

There have been few series reporting outcomes of pregnancy among patients abusing methamphetamines. Adverse perinatal outcomes have been reported in Scandinavian methamphetamine addicts, including increased rates of preterm birth, intrauterine growth retardation, placental abruption, and fetal distress.[8,9] Three major studies have addressed methamphetamine use in pregnancy in US centers. One found associations with prematurity and low birth weight.[10] The other two showed reduced birth weights relative to the normal obstetric population, but reported no other excesses of adverse outcomes.[11,12] The concern has been raised that babies with exposure to either methamphetamines or cocaine in utero are at risk for intracranial lesions, including intraventricular hemorrhage.[3,13]

Individual case reports raise additional concerns, particularly regarding maternal risks of amphetamine abuse. Amphetamines have been reported to cause cardiovascular collapse during anesthesia for cesarean section.[14,15] The mechanism presumably involves the depletion of epinephrine and norepinephrine reserves, so that the maternal compensatory response to regional anesthesia may be impaired. Amphetamine use has also reportedly caused seizures mimicking eclampsia.[16] These reports were published before the widespread availability of crystal in this country.[14-16] We are not aware of previous reports of obstetric deaths attributed to methamphetamine abuse.

Did amphetamine abuse actually cause the two deaths reported here? Patient 1 arrived at the hospital with tumultuous labor and thick meconium, factors that are often present in amniotic fluid embolism. It has been argued that amphetamines promote uterine hyperactivity by increasing norepinephrine release.[10] This phenomenon has not been investigated in animal models. Cocaine, however, has been shown in vitro to abruptly increase uterine activity; α-adrenergic stimulation and the inhibition of β-receptors (both of which also occur with amphetamine use) are proposed mechanisms.[17] In our experience, hypertonic uterine activity is common in women using amphetamines. We speculate that, in patient 1, methamphetamine use promoted the hypertonic uterine contractions and was a contributing cause of the amniotic fluid embolism.

Patient 2 had the HELLP syndrome, and a massive intracranial hemorrhage caused her death. Intracranial hemorrhage may occur in preeclampsia or in eclampsia, with or without thrombocytopenia. The most common lesions on radiography and at autopsy are petechial hemorrhages, but large hemorrhages occasionally occur.[18-20] In the older obstetric literature and among women in developing countries, intracranial hemorrhage has been reported to be among the most common causes of death in preeclampsia or eclampsia.[20,21] Among recent series in the United States, however, intracranial hemorrhage rarely caused maternal death. For example, among a total of 499 cases of eclampsia reported in two large institutions, 2 maternal deaths occurred, 1 from cardiac arrest before the patient arrived at the hospital and 1 due to magnesium toxicity.[22,23] Among 499 cases of the HELLP syndrome reported from the University of Arizona and the University of Tennessee at Memphis Medical Centers, there were 7 maternal deaths, none due to intracranial hemorrhage.[24,25] In a ten-year experience at tertiary care referral centers caring for more than 60,000 pregnancies, we have encountered 4 other maternal deaths in cases of preeclampsia or eclampsia, none due to intracranial hemorrhage.

Although the cause of the intracranial hemorrhage in patient 2 could have been preeclampsia or eclampsia, intracranial bleeding is also a common complication of methamphetamine abuse.[26] The location of the hemorrhage is far more characteristic of amphetamine abuse than of preeclampsia or eclampsia. Blood pressure fluxes following the patient's use of crystal likely caused the hemorrhage, or at least contributed to the development of bleeding, and therefore the patient's death.

These two maternal deaths occurred among about 22,000 deliveries at the Mary Birch Hospital for Women at Donald N. Sharp Memorial Community Hospital and the Women's Center at Grossmont Hospital in 1992 and 1993. During the same time, the perinatology group serving the Sharp Hospital system and the San Diego community saw numerous additional serious obstetric complications in pregnant women abusing methamphetamines. Apart from patient 2, we cared for two patients with intracranial hemorrhage during the third trimester of pregnancy; one of the two was "high" on "ice" at admission and was a long-term abuser of crystal methamphetamine. We saw two women with cardiovascular collapse following regional anesthesia for delivery. Both required resuscitation with high doses of pressors for prolonged periods of time, and both proved to be long-term users of crystal methamphetamine. Neither patient had underlying medical problems apart from the drug abuse. We also treated three cases of methamphetamine-induced hypertensive crisis and one patient with a grand mal seizure following crystal methamphetamine abuse during the third trimester of pregnancy.

If the statewide prevalence figure of 0.66% is applicable to our referral base of approximately 25,000 deliveries per year, these obstetric problems occurred among approximately 330 amphetamine users. It should be recognized, of course, that our perinatology group is not asked to consult for all serious problems involving the referral base.

The true rate of methamphetamine-related obstetric complications remains to be elucidated by a prospective population-based study. Our experience, however, suggests that methamphetamine use presents a great danger to pregnant women.

How should this information be integrated into obstetric practice? First, obstetric care providers need to be aware of the prevalence of the problem and of the epidemiologic risk factors for amphetamine abuse during pregnancy. We must be willing to test patients who have high-risk characteristics and to educate them regarding the risks of methamphetamine use. Second, clinicians must have a high index of suspicion for drug abuse in evaluating patients with obstetric complications such as hypertensive crisis, abruption, preterm labor, or maternal intracranial hemorrhage. Third, both obstetricians and anesthesiologists need to be aware of the possible interactions of routine medications, such as terbutaline sulfate for hypertonic contractions or preterm labor and regional anesthesia for labor in amphetamine users.

Unfortunately, women who are at highest risk to use crystal often do not seek prenatal care, patients who are identified during their prenatal care as using this drug may withdraw from care, and even highly motivated patients may be unable to control their desire for this highly potent psychoactive and vasoactive drug.

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